duced bone loss. The effects on the PbB of Pb in drinking water (PbW), Pb released from bones, and change in lead exposure before, during, and after spaceflight were evaluated using a physiologically based pharmacokinetic (PBPK) mathematical model (2013, Aviation, Space, & Environmental Medicine 84:1229-1234) that incorporates environmental lead exposure on earth and in flight and includes temporarily increased rates of osteoporosis during spaceflight. The model predicts that the average American astronaut in 2030 (the earliest anticipated launch date for a long-duration mission) would have a PbB of 1.7 μg/dL at launch and that PbB levels would decrease in microgravity at PbW values less than about 9 μg Pb/L because of reduced lead exposure during spaceflight. Currently, PbW on the International Space Station (ISS) averages <1 μg Pb/L. A SWEG of 9 μg Pb/L would protect most astronauts on long-duration spaceflights by ensuring that PbB values will not exceed pre-launch levels. At in-flight PbW concentrations <9 μg Pb/L, Pb concentrations in both bone and blood would gradually decrease below their pre-launch values. On the other hand, astronauts who have high concentrations of lead stored in bones (an unlikely possibility) could experience increased PbB levels in microgravity due to release of lead from bones. While the resultant in-flight PbBs would depend on their pre-flight bone lead levels, their PbBs will not be significantly further elevated (<1 μg/dL) by consuming water with a PbW of ≤9 μg /L. Because individuals with a history of clinical lead poisoning would likely have high concentrations of lead stored in their bones, we recommend that such individuals avoid exposure to microgravity of more than a few days' duration to prevent in-flight lead poisoning.

PS 632e Using Pharmacokinetic Modeling to Derive Infant: Mother Internal Exposure Ratios for the Prediction of Infant Exposure to POPs throughout Breastfeeding

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It is now well established that breastfeeding is a major source of exposure to persistent organic pollutants (POPs) in newborns and infants. These chemicals are eliminated very slowly and can rapidly accumulate in infants. Infant internal exposure may even exceed maternal levels during the breastfeeding period. Some studies suggest that high exposure to these chemicals at such a critical time in infant development can lead to certain problems later in life, hence the increasing attention in risk assessment. One of the major problems is the estimation of this exposure in children. The objective of this study was to estimate the maximal internal exposure an infant can attain compared to its mother. Using a validated pharmacokinetic model for POPs, Monte-Carlo simulations were performed to obtain distributions of infant:mother internal exposure (IMIE) ratios and these were compared to available data from a cohort where POP levels were measured in mothers at delivery and their 6-month-old infants (HCB and PCB-153). While not being overly conservative, the calculated maximal IMIE (Max IMIE) ratios were greater than all measured IMIEs of dyads that were strictly breastfed before blood measurement (n=50 per chemical). For example, the Max IMIE at 6 months of age is estimated to be 6.61 for HCB (Median=2.94) and 6.85 for PCB-153 (median=3.00) while the observed values were below the estimated 95th-ile. The peak Max IMIE is attained at 12 months and reaches 16.9 for HCB and 19.1 for PCB-153. A series of Max IMIEs were then estimated to compounds of different half-lives and for infants breastfed from birth to 24 months of age. The Max IMIE is a new exposure factor that could easily be applied in risk assessment when estimating infant exposure to breast milk with prior knowledge of maternal exposure.

PS 632f The Toxic Potency of 2, 3-Pentanedione Relative to Diacetyl

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Diacetyl is often used in the food flavoring and production industries and occupational exposure to this substance has been associated with severe respiratory responses in workers. 2,3-Pentanedione (PD) has been used as a substitute for diacetyl; it is also of concern because of its structural similarities and because toxicological studies show similar pathologic responses in the upper and lower respiratory tracts of experimental animals. An earlier analysis of the relative toxic potency of PD and diacetyl was based on pilot study data (n=5 per dose group) for diacetyl, in male mice only. This analysis presents an updated comparative potency analysis of PD relative to diacetyl, based on new data for diacetyl. A 2-week + 2 day inhalation study of rats and mice exposed to PD (n=6 per dose group) was compared to a recent 13-week NTP study of diacetyl in male and female mice and rats (n=10 per dose group), as well as the male mouse pilot study data. The results are based on multinomial regression modeling of severity-ordered pathological response data. Benchmark concentrations (BMCs) for lesion scores of 1+ (at least minimal) were estimated for those models having a significant dose-response (P<0.05) and an adequate fit (P>0.05). A more complex model was necessary for estimating mouse BMCs, in which quadratic dose terms significantly improved the fit, and adjustments for the different durations of these studies were incorporated. The relative potency estimates (diacetyl/PD) range from 0.81–7.3, depending on sex and the specific endpoint evaluated (where 1.0 would indicate equal toxic potency for the two compounds). Model-based 95% confidence limits range from 0.55–14, and the range increased to 0.44–21 when adjusted for overdispersion. These results suggest that equal or greater toxic potency for PD relative to diacetyl cannot be ruled out on the basis of currently available data.

PS 632g Dose-Response Assessment of the Nephrotoxicity of Melamine and Cyanuric Acid in Rodents—A Summary of Studies Conducted at the US FDA

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In 2007, the intentional adulteration of pet food ingredients with melamine and cyanuric acid, caused kidney failure and death of hundreds of cats and dogs in the U.S.. Early investigation revealed that co-exposure to these compounds can elicit nephrotoxicity due to the formation of highly insoluble melamine cyanurate (MC) crystals in the nephrons. In response to these events, and later events in China in 2008 involving the contamination of infant formula with melamine, it became apparent to regulatory agencies, including the U.S. Food and Drug Administration (FDA), that further in-depth studies addressing the toxicity of melamine, cyanuric acid, and their combination were warranted. We report the design and outcome of 7- and 28-day feed, and 90-day gavage dose-response studies conducted at the FDA in male and female F344 rats on the combined nephrotoxicity of melamine and cyanuric acid. The current tolerable daily intakes (TDI) established by the FDA for dietary exposure to melamine and its derivatives are based upon a NOAEL of 63 mg/kg bw/day for dietary exposure to melamine in a 13-week rat study. The data from our current studies demonstrate that in F344 rats, oral co-exposure to melamine and cyanuric acid results in a NOAEL value 25- (based upon renal histopathological alterations such as tubule degeneration, fibrosis, dilatation and epithelium hyperplasia and elevated blood urea nitrogen and serum creatinine) to 100-fold (based upon MC crystal formation) lower than that previously considered in the risk assessments based on the NOAEL value derived from exposure to melamine alone.

PS 632h Proposed Novel Method for Assessing Risks of Inhaled Titanium Dioxide from Cosmetics

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Titanium dioxide (airborne, unbound particles of respirable size) was added to the Proposition 65 list in 2011 as a carcinogen. Numerous notices of violation (NOV) have since been filed against cosmetic products. High dose studies show TiO2 induces lung tumors in rodents but epidemiology studies fail to show this association even with years of occupational exposure. The cancer mechanism is thought to be overloading of lung clearance due to the poorly soluble respirable particles. A Safe Harbor Level (SHL) for TiO2 has not been derived by OEHHA; however, Prop 65 regulations allow for SHL to be derived according to scientific methods. Route-appropriate (i.e., inhalation) human SHLs based on occupational data have been determined for assessing risk from cosmetics use using products with highest potential consumer exposures to TiO2: aerosol hairsprays and sunscreens. SHLs were adapted based on occupation exposure levels shown not to over burden the lungs or increase cancer risk over the course of a 40 year working career. The amortized SHLs correspond to 55, 13, and 1.6 mg/day, for TiO2 (total), fine, and ultrafine, respectively. Respirable particles (<10 μm size), may cover most of the TiO2 particles present in sunscreens; however, only about 5% of airborne particles created during spraying would be expected to be of respirable size. Thus, using data on frequency of use and use levels from survey data on cosmetics and scientifically-based exposure assessment calculations, the exposure to TiO2 would be 0.82 mg/day for hairspray and 0.32 mg/day for spray sunscreen, which are below all SHLs. TiO2 exposures from other cosmetic products such as compacts that are not aerosolized would be even lower. As such it is evident that the NOV filed against these various products are unwarranted as users would not be exposed to TiO2 levels that would cause cancer even allowing for daily lifetime applications. This work further underlines the importance of science-based decision-making in relevant risk communication in the public domain.

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